at least one supply mechanism for introducing the culture medium into the plurality of culture containers and for discharging the culture medium from the plurality of culture containers; and

wherein a common culture medium supply line connected to the plurality of culture containers communicates with a riser on which at least one level sensor is carried, the sensor being vertically adjustable relative to said riser to sense a level of the culture medium for the plurality of culture containers, and wherein the sensor controls the supply mechanism as a function of an output signal of the level sensor representing the level of the culture medium such that a submerged culture medium supply condition and a basal culture medium supply condition can both be achieved by the device, the basal culture medium allowing that the cultured cells on said cell culture insert can homogeneously be exposed to gases, aerosols and particulate matter.--.

REMARKS

Claims 1-27 were pending in the application. By this paper, claims 1 and 3-27 remain pending, claim 2 has been canceled without prejudice, claims 1 and 11 have been amended, and new claim 32 has been added for consideration. Reconsideration and withdrawal of the objections and rejections are respectfully solicited in view of the foregoing amendments and the following remarks.

Drawing Objections

The drawings have been objected to for containing informalities in the enlargements shown in FIGS. 1, 2, and 4. Proposed corrected drawings are submitted herewith under separate cover in a document entitled "Submission of Proposed Corrected Drawings." FIGS. 1, 2, and 4 have been amended to be identified as FIGS. 1a, 2a, and 4a. The respective enlargements have been labeled FIGS. 1b, 2b, and 4b.

Upon acceptance of the proposed corrections, the applicants will submit appropriate substitute formal drawings. The specification has been appropriately amended herein to reflect these drawing corrections. No new matter has been entered either in the drawings or the specification.

Claim Rejections - 35 U.S.C. §102

Claims 1 and 3 have been rejected under §102(b) as anticipated by Liau et al., GB 2 314 343 A (Liau). Independent claim 1 has been amended herein to recite a cell culture

insert *providing a horizontal culture surface*. Claim 1 also recites that, based on the sensor controlling the culture medium supply mechanism, the device can achieve a *basal culture medium supply condition*. The basal condition is recited as permitting the cultured cells on the horizontal insert to be *homogeneously exposed to gases, aerosols, and particulate matter*.

Liau fails to disclose or suggest at least these features of amended claim 1. In contrast, Liau discloses only **vertical** cell culture inserts. Such vertical inserts are only suited for a *short exposure* to oxygen, when the cell culture medium is removed. With the vertical cell culture inserts, a homogeneous exposure to a medium of cells adhering to the **vertical** inserts cannot be achieved, such as, for example, an aerosol medium comprising particulate matter or a particulate matter medium alone whose influence on the cultured cells is to be studied. The Liau device is not well suited for basal culture medium supply conditions. In contrast to Liau, the structure of amended claim 1 allows a homogeneous deposit of and interaction with such substances and permits basal culture medium supply conditions.

Thus, Liau fails to disclose or suggest all of the limitations of amended claim 1. Claim 1 and dependent claim 3 are neither anticipated nor rendered obvious by the teachings of Liau.

Claims 1, 3, 12, and 25 have been rejected as anticipated by Kolodii et al., SU 734,281 B (Kolodii). Kolodii fails to disclose a cell culture *insert*, regardless of orientation. Instead, Kolodii teaches use of a **packing** on which the cells are cultured. This is clearly set forth in the abstract of Kolodii. Kolodii does not disclose use of cell culture *inserts*, nor such inserts providing a *horizontal* culture surface suitable for basal culture medium supply conditions. Kolodii fails to disclose or suggest the same limitations of claim 1 noted above as also missing in Liau.

Thus, Kolodii fails to teach or suggest all of the limitations of amended claim 1. Claim 1 and dependent claims 3, 12, and 25 are neither anticipated nor rendered obvious by the teachings of Kolodii.

Claims 1, 3-5, 7, 11, 12, 21, 22, and 25 have been rejected as anticipated by Geimer et al., U.S. Patent No. 4,639,422 (Geimer). Geimer also does **not** describe a cell culture *insert* of any kind, much less one having a *horizontal* culture surface. In contrast, Geimer teaches, at column 2, line 68 through column 3, line 1, a cell culture filter vessel with a vertically oriented filter unit. The filter unit is disclosed as useful in the **continuous suspension culture** of mammalian cells, or such cells with **carrier particles** on which the cells are

attached (see column 2, lines 10-12). Geimer does not disclose use of cell culture inserts having horizontal culture surfaces suitable for basal medium supply conditions. Geimer fails to disclose or suggest the same limitations of claim 1 noted above as also missing in Liau and Kolodii.

Thus, Geimer fails to teach or suggest all of the limitations of amended claim 1. Claim 1 and dependent claims 3-5, 7, 11, 12, 21, 22, and 25 are neither anticipated nor rendered obvious by the teachings of Geimer.

In view of the foregoing, the anticipation rejections based on Liau, Kolodii, and Geimer should be withdrawn.

Claim Rejections - 35 U.S.C. §103

Claims 1-27 have also been rejected under 35 U.S.C. §103(a) as obvious over each of Liau, Kolodii, and Geimer in view of one or more of Shuler et al., U.S. Patent No. 5,612,188 (Shuler), Japanese document no. JP 02 119 772 (JP 772), or Kearney, U.S. Patent No. 5,424,209 (Kearney). Claim 2 has been canceled herein.

The action admits at page 5, paragraph 3, that neither Liau, Kolodii, nor Geimer teach a horizontal culture surface among other limitations. Additional limitations missing from these references are discussed above. Neither Shuler, JP 772, nor Kearney provide any disclosure of the same missing limitations discussed above.

To illustrate, Shuler does not mention a cell culture insert at all. Further, Shuler is silent as to any culture surface or surface orientation. The culture chambers or containers 56 and 68 are only generally identified and discussed. The culture containers in Shuler are operated *without cell culture inserts* and are, therefore, not suited for a basal culture medium supply. Shuler fails to provide the same limitations missing in each one of Liau, Kolodii, and Geimer.

JP 772 discloses a high concentration **suspension** culture that is employed *without a cell culture insert*. JP 772 fails to disclose a cell culture insert, much less one having a horizontal culture surface. Exposing cultured cells to gases or aerosols or particulate matter (e.g., pollutant gases) is not addressed in JP 772. This is because it would be impossible with the culture of the device of JP 772 to homogeneously expose the cells directly to gases, for example, over a prolonged time, since the cells would be without a cell culture medium

supply. Thus, no basal culture medium supply is possible in the device of JP 772. JP 772 fails to provide the same limitations missing in each one of Liau, Kolodii, and Geimer.

Kearney also does not mention a cell culture insert or culture surface of such an insert. The culture containers in Kearney are operated without cell culture inserts and, therefore, are also not suited for a basal culture medium supply. Kearney also fails to provide the same limitations missing in each one of Liau, Kolodii, and Geimer.

Since none of the cited references discloses a cell culture *insert* that utilizes a *horizontal* culture surface by which a basal culture medium supply condition is achievable, no combination of these references renders obvious independent claim 1 or dependent claims 3-27.

As noted in paragraphs 1 and 3 of the applicants' own specification, conventional culturing devices, such as those disclosed in the cited references, are limited for use in submerged culture systems, i.e., not suited for basal culture medium supply conditions.

In contrast, amended claim 1 recites a device that advantageously permits control of a culture medium level via a level sensor, wherein the medium can be supplied to cells not only in a submerged culture condition, but also in a basal culture medium supply condition. This allows the cells to be homogeneously exposed to gaseous, liquid, or particulate substances whose influence on the cell is to be studied without interrupting the supply of culture medium.

New claim 32

New claim 32 had been presented for consideration. Claim 32 is similar in scope to amended claim 1, but further recites a plurality of culture containers being positioned so that the horizontal culture surface provided by each of the culture containers lie in a common horizontal plane. Claim 32 also recites a common culture medium supply line connected to the plurality of culture containers. The supply line is recited as communicating with a riser on which at least one level sensor is carried, the sensor being vertically adjustable relative to said riser to sense a level of the culture medium for the plurality of culture containers. No such device is disclosed or suggested in any of the cited references, whether taken alone or in combination. Claim 32 is believed to be in condition for allowance.

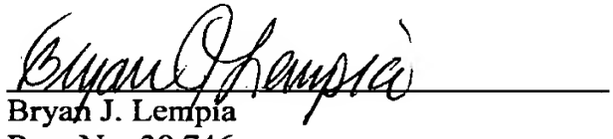
CONCLUSION

Claims 1 and 3-27 and new claim 32 are believed to be in condition for allowance in view of the foregoing amendments and remarks. Withdrawal of the rejections and allowance of the claims are respectfully solicited.

The examiner is invited to contact the undersigned at the telephone number listed below in order to discuss any remaining issues or matters of form that will move this case to allowance.

No fee is believed due at this time. Thirty-one claims have previously been paid for, and by this paper, only two independent claims and 27 claims are pending. However, the Commissioner is hereby authorized to charge any fee deficiency, or credit any overpayment, to Deposit Account No. 13-2855 of the undersigned.

Respectfully submitted,

By: 

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VERSION SHOWING CHANGES MADE

In the Drawings

Proposed corrected drawing figures 1a, 1b, 2a, 2b, 4a, and 4b are submitted herewith under separate cover in a document entitled "Submission of proposed Corrected Drawings." Changes to the drawings are shown in red ink.

In the Specification

Please amend the figure descriptions at page 5, lines 7-16, as follows:

Figure 1a is a schematic view of a culturing device constructed in accordance with the teachings of the invention and utilizing only one culture container [the] that has a controllable culture medium level;

Figure 1b is an enlargement of the device taken from circle 1b in Figure 1a;

Figure 2a is a schematic view of another culturing device constructed in accordance with the teachings of the invention;

Figure 2b is an enlargement of the device taken from circle 2b in Figure 2a;

Figure 3 is a top view of another culturing device constructed in accordance with the teachings of the invention and utilizing a number of culture modules placed parallel to one another, each having a number of culture containers;

Figure 4a is a longitudinal section taken along line IV-IV through a culture module of the culturing device shown in Figure 3;

Figure 4b is an enlargement of the device taken from circle 4b in Figure 4a;

Please amend the last full paragraph at page 5, lines 28-31, as follows:

Referring now to the drawings, Figure 1a illustrates an entire culture unit 10 having a culture container 12. The illustrated culture unit 10 is generally in the form of an inverted bottle. The upper end of the culture unit 10 defines a circular opening 14.

Please amend the paragraph bridging pages 5 and 6 as follows:

A cell culture insert 15 is placed inside the culture container 12 and is produced from a porous synthetic material, such as for example, polyethylene terephthalate. The cell culture insert 15 has a liquid-permeable carrier structure or membrane 16, which can be produced from the different synthetic materials, depending on the requirements of the cells to be cultured, again such as for example, polyethylene terephthalate. As is shown in Figure 1b taken from the enlarged portion of Figure 1a, the membrane 16 supports and carries a cell culture 18.

Please amend the first full paragraph at page 6, lines 5-7, as follows:

The culture container 12 is carried by a holding device 20. The structure of the device 20 can vary considerably and is therefore only indicated schematically in Figure 1a.

Please amend the second to last paragraph at page 6, lines 15-27, as follows:

Two control terminals of the pump 24 are respectively connected through power amplifiers 32 and 34 to the outputs of an operating circuit 36. The operating circuit 36 produces a signal at a first, a second or neither of its outputs in order to actuate the pump 24. The pump can introduce additional culture liquid from the storage container 28 to the inside of the culture container 12 or can remove culture liquid from the inside of the culture container 12 and return it to the storage container 28. The pump function depends on the output signal of a continuously operating level sensor 38 that is shown as a sensor mounted to the outside surface of the culture container 12. Alternatively, the sensor can also be mounted on the inside surface of the culture container 12. The sensor 38 can be an optical sensor in practice and operate as a function of a target value transducer 40, which is shown as an adjustable resistor. The target value transducer 40 can be adjusted by a programmed controller 42 as indicated in Figure 1a by a dotted line.

Please amend the first two paragraphs at page 7, lines 1-7, as follows:

The target value transducer 40 is switched to the second position by the programmed controller 42 to correspond to a liquid level shown in Figure 1a by the dotted line 44. In this

position, the liquid level is above the peaks of the cell culture 18. This condition is a submerged nutrient supply system.

A practical example shown in Figure 2a corresponds largely to the example shown in Figure 1a. The corresponding components have the same reference number and will not be explained further in detail.

Please amend the first paragraph at page 8, lines 1-8, as follows:

The supply lines 62 of the various culture modules 58 are each connected through tubing 64 to a corresponding discharge connector 66 of a culture medium distribution system 68. The tubing 64 is shown only schematically in Figure 3, and can optionally be produced from a material such as silicone. The culture medium distribution system 68 is connected to a supply of culture medium by a supply connector 70. Similar to the practical examples shown in Figures 1a and 2a, the supply connector 70 is connected to the discharge of a culture medium pump 24 or 24', also with conventional tubing such as silicone tubing (not shown).

Please amend the first full paragraph at page 11, lines 5-16, as follows:

In Figures 1a and 2a, the cell culture inserts 15 are shown schematically as being incorporated as part of the container 12 substrates in order to simplify the drawings. However, in practice, the cell culture inserts 15 are preferably not fixed in the culture containers 12, but rather are preferably discrete parts that can be removed from the containers. As indicated in Figure 4 for a culture container 12, a commercial cell culture insert 122 can be in the shape of a cylindrical beaker with a flat bottom wall 124 and a cylindrical peripheral wall 126. By placing the cell culture inserts 122 into the culture container 12 and securing or supporting them with the aid of the glass bridges 57, the various bottom walls 124 can be assured to lie in a common horizontal plane. The cell culture inserts 122 may optionally [bel] be made of a porous synthetic material as can the cell culture inserts 15 in Figures 1a and 2a.

Please amend last full paragraph at page 13, lines 13-16, as follows:

A culturing device is shown in Figures 3 to 7 with its own temperature-control device. However, the device of Figures 3 to 7 can be provided without temperature-control, similar to the culturing devices shown in Figures 1a and 2a. Such a device can simply be placed into a temperature-control cabinet.

In the Claims

Please cancel claim 2 without prejudice herein, amend claims 1 and 11, and add new claim 32 as follows:

1. (Amended) A culturing device comprising:

at least one culture container adapted to receive and to discharge a culture medium;

a cell culture insert removably received and providing a horizontal culture surface within the at least one culture container;

at least one supply mechanism for introducing the culture medium into the at least one culture container and for discharging the culture medium from the at least one culture container; and

at least one level sensor cooperating with the at least one culture container to sense a level of the culture medium for the at least one culture container, wherein the sensor controls the supply mechanism as a function of an output signal of the level sensor representing the level of the culture medium such that a submerged culture medium supply condition can be achieved by the device, and that a basal culture medium supply condition can [both] be achieved by the device allowing that the cultured cells on the cell culture insert can homogeneously be exposed to gases, aerosols and particulate matter.

11. (Amended) A culturing device as defined in claim 10, wherein at least one of the level sensors continuously measures the culture medium level.

Please add new claim 32 as follows:

--32. A culturing device comprising:

a plurality of culture containers adapted to receive and to discharge a culture medium;

cell culture inserts, one for each of the plurality of culture containers removably received within the culture containers, the cell culture inserts each providing a horizontal culture surface wherein the plurality of culture containers are positioned so that the horizontal culture surface provided by each of the culture containers lie in a common horizontal plane;

at least one supply mechanism for introducing the culture medium into the plurality of culture containers and for discharging the culture medium from the plurality of culture containers; and

wherein a common culture medium supply line connected to the plurality of culture containers communicates with a riser on which at least one level sensor is carried, the sensor being vertically adjustable relative to said riser to sense a level of the culture medium for the plurality of culture containers, and wherein the sensor controls the supply mechanism as a function of an output signal of the level sensor representing the level of the culture medium such that a submerged culture medium supply condition and a basal culture medium supply condition can both be achieved by the device, the basal culture medium allowing that the cultured cells on said cell culture insert can homogeneously be exposed to gases, aerosols and particulate matter--.